DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-395

Boehringer Ingelheim Pharmaceuticals, Inc.
P.O. Box 358
Ridgefield, CT 06877-0368

Attention: Peter Fernandes, M.Pharm.
Director, Drug Regulatory Affairs

Dear Mr. Fernandes,

Please refer to your new drug application (NDA) dated December 12, 2001, received December 13, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Spiriva HandiHaler (tiotropium bromide inhalation powder).

We also refer to your amendments dated March 25, April 2, 12, and 18, July 16, 24, 25(2), and 31, August 6, September 18 and 24, October 2, and November 19, 2002; July 31, August 22, October 24, November 5, and December 11, 16, and 30, 2003; and January 5, 8, 14, 15, 22 and 26, 2004.

The July 31, 2003, submission constituted a complete response to our December 20, 2002, action letter.

This new drug application provides for the use Spiriva HandiHaler (tiotropium bromide inhalation powder) for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and patients instructions for use dated January 26, 2004) and submitted labeling (immediate container and carton labels submitted January 8, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-395**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of the postmarketing study commitments you made in your submission dated January 15, 2004. These commitments are listed below.

1. A randomized, double-blind study including both a placebo-control arm and a positive-control arm to evaluate the effect of tiotropium on the QT interval.

Protocol Submission:	June 30, 2004
Study Start:	December 31, 2004
Final Report Submission:	December 31, 2005

2. A 13-week inhalation study in Wistar rats to qualify the degradants(b)(4)---------- (b)(4)---------- according to current ICH guidelines. The test articles will be (b)(4)---------- with the individual degradants. The aerosol quality (b)(4)----------–--- will be sufficient to provide an estimated lung dose at least 10 fold higher than that estimated for humans administered daily with 22 µg tiotropium bromide monohydrate.

Protocol Submission:	March 31, 2004
Study Start:	June 30, 2004
Final Report Submission:	December 31, 2004

Submit clinical protocols to your IND for this product. Submit nonclinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

We also remind you of the outstanding chemistry, manufacturing, and control agreements in your submission dated January 5, 2003. These agreements are listed below.

A. To report the actual (b)(4)---levels found (in ppm) on the Certificates of Analysis for Tiotropium Bromide Monohydrate drug substance.

B. To collect confirmatory microscopic examination data on the first three production stability batches of drug product and to include (b)(4)---------- (b)(4)---------- ---------- ---------- ----------

C. To print a unique batch number on the outer carton for traceability of the Handihaler device and the Spiriva capsules in addition to the lot number of packaged capsules and the expiry date of the capsules.

D. To pursue further investigations into validating the (b)(4)-------- for the determina tion of moisture content. Single capsule determinations will be implemented if the system is shown to have the required specificity and is demonstrated to be suitable for single capsule determinations. If specificity is demonstrated, but the precision for single capsule determinations is inadequate, BI will reduce the number of capsules tested to the smallest amount supported by validation data. If suitability can be successfully demonstrated, BI will:

- Include (b) determinations in any stability studi es supporting the registration of the (b)(4)-(b)(4)----------
- Justify appropriate release and shelf-life specifications for moisture content based on representative batch release and stability data.
- Implement (b)(moisture determinati ons into the drug product testing specification for the (b)(4)---------- (b)(4)----------

E. b)(4)----------

F. To monitor and investigate any problems with the capsules (e.g., significant damage to capsules after piercing) on stability, as per the Post-Approval Stability Protocol, and to discuss them with the FDA.

G. To provide aerodynamic particle size distribution data from the ongoing stability study in the (b (b)(4)----------as soon as they are available after samples are analyzed at each time point.) ---------- - -------ent with the protocols for the ongoing studies, an updated 9-month stability report by the end of February 2004, and to provide a 12-month stability report by the end of May 2004. If these future stability data show that there is a real trend of (b)(4)---------- (b)(on stability at 25°C/60% r .h. or (b)(4)----------, to discuss the findin-- ---------- as soon as possible, and to thoroughly investigate the findings. Data from stability studies at 40°C/75% r.h. will be reported but not factored into any assessment of significant change in

APSD for the drug product,(b)(4)----------(b)(4)---------- -

H. To provide an updated Methods Validation package. The package will include a listing of all samples and standards to be submitted together with certificates of analysis and material safety data sheets for each sample and standard provided.

I. To investigate, rectify, and discuss with the Agency any unusual variability of the PSD results for (b)(4)------ tiotropium bromide monohydrate after b)(4) ----------(b)(4)----------

J. In the performance of the aerodynamic particle size distribution testing for the drug product, to assess by further testing b)(4)---------- is due to drug product. If drug product failure is confirmed, these results will be discussed with the Agency.

K. To submit to this NDA, the test procedure and validation report for degradant(b)(4)------by the end of February 2004, along with a revised post-approval stability protocol and stability agreement.

Please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

As discussed during the telephone conversation on January 30, 2004, between Mr. Peter Fernandes, Boehringer Ingelheim, and Mr. Anthony Zeccola, Division of Pulmonary and Allergy Drug Products, we request you make the following changes to the carton labeling and the patient instructions for Spiriva HandiHaler at the time of the next printing:

1. The following comments pertain to the CARTON LABELING:

   a. On the principal display panel, relocate the strength [i.e., 18 mcg (as tiotropium) per capsule] so that it immediately follows the established name.

   b. On the principal display panel, relocate the statement “Spiriva® capsules for use with HandiHaler® only” so that it is presented immediately after the words “FOR ORAL INHALATION ONLY.”

   c. Decrease the size of the turquoise and green color blocks on the principal display panel to allow for more space for the proprietary and established names and other important information.

   d. Increase the prominence of the established name on the principal display panel.

   e. Increase the prominence of the statement “Open the blister foil as far as the *STOP* line to expose only capsule at a time.”

2. The following comments pertain to the PATIENT’S INSTRUCTIONS FOR USE:

   a. Under the heading “**Removing Spiriva from the blister**”:

      (1) Sections B and C are redundant. Consolidate these two sections to enhance readability. Increase the prominence of the sentence "If additional capsules are inadvertently exposed to air, they should not be used and should be discarded" and make it into a separate paragraph.

      (2) Either delete picture C or give it a different instruction, such as "Remove the capsule from the blister."

      (3) Maintain the paragraph "**Do not store capsules in the HandiHaler device**" at the end of section C or the end of section B, if section C is deleted.

   b. Under the heading “**Taking your dose of Spiriva**”:

      (1) Revise section 5 to read "Breathe out completely. (Figure 5) Important: Do not breathe (exhale) into the mouthpiece at any time."

      (2) Section 6 states “. . . breathe in slowly and deeply but at a rate **sufficient to hear the capsule vibrate**.” Clarify what is to be done if you do not hear the capsule vibrate (e.g., take another dose; do not take another dose, etc.)

      (3) Section 7 states “Tip out the used capsule and dispose . . . ” Where and/or how should the user dispose of the empty capsule?

As discussed, please submit a labeling supplement well enough in advance of your anticipated next printing so that there will be adequate time available for review by the Agency.

If you have any questions, call Anthony M. Zeccola, Regulatory Management Officer, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Robert Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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